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(FILE 'HOME' ENTERED AT 09:07:30 ON 01 JUN 2006)

FILE 'CAPLUS, BIOSIS, MEDLINE' ENTERED AT 09:08:07 ON 01 JUN 2006

L1 644567 S INSULIN
L2 2280313 S DERIVATIVE?
L3 9988 S L1 (L) L2
L4 66761 S LIPOPHIL?
L5 92 S L3 (L) L4
L6 51 DUP REM L5 (41 DUPLICATES REMOVED)
L7 39 S L6 AND PY<2002
L8 145 S L3 AND HEXAMER?
L9 102 DUP REM L8 (43 DUPLICATES REMOVED)
L10 71 S L9 AND PY<1998
L11 59 S L10 AND PY<1996
L12 0 S L9 AND LIPOPHILIC
L13 0 S L9 AND LIPOHIL?
L14 3 S L9 AND LIPO?
L15 0 S L5 AND HEXAMER?
L16 19 S L5 AND STAB?
L17 0 S L16 AND PROLOGN
L18 0 S L16 AND LIFE
L19 1 S L16 AND TERMIN?
 E MARKUSSEN JAN /AU
 E HAVELUND SVEND /AU
L20 88 S E3
 E MARKUSSEN JAN /AU
L21 116 S E3
 E BRANDT JAKOB /AU
L22 44 S E3
 E HANSEN PETER /AU
 E KURTZHALS PETER /AU
L23 44 S E3
L24 33 S L20 (L) L21
L25 3 S L22 (L) L23
L26 3 S L24 AND L22
L27 15 S L24 AND L23
L28 10 DUP REM L27 (5 DUPLICATES REMOVED)
L29 5 S L28 AND INSULIN AND DER?

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L29 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Insulin derivatives
IN Markussen, Jan; Jonassen, Ib; Havelund, Svend; Brandt,
Jakob; Kurtzhals, Peter; Hansen, Per Hertz; Kaarsholm, Niels
Christian
PY 1996
1996
1996
2000
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1998
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2002
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2003
2004
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
TI Insulin derivatives
IN Markussen, Jan; Jonassen, Ib; Havelund, Svend; Brandt,
Jakob; Kurtzhals, Peter; Hansen, Per Hertz; Kaarsholm, Niels
Christian
AB Insulin derivs. in which a lipophilic group having
from 12 to 40 carbon atoms is attached to the α -amino group of the
. . . the carboxy group of the C-terminal amino acid in the B-chain have a
protected profile of action. Thus, LysB30(N ϵ -tetradecanoyl)ThrB29
human insulin was prepared via polymerase chain reaction (PCR) and
reaction with tetradecanoic acid N-hydroxysuccinimide ester.
ST insulin tetradecanoyl prepns
IT 11061-68-0DP, Human insulin, derivs. 184181-38-2P
184181-40-6P 184181-41-7P 184181-43-9P 184181-44-0P 184181-47-3P
184181-61-1P
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP
(Preparation)
(preparation of insulin derivs.)
IT 184181-45-1P 184181-49-5P 184181-50-8P 184181-51-9P 184181-52-0P
184181-54-2P 184181-56-4P 184181-59-7P 184181-62-2P 184181-64-4P
184246-94-4P
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological
study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of insulin derivs.)
IT 184181-53-1P 184181-55-3P 184181-57-5P 184181-60-0P 184181-63-3P
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic
preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant
or reagent)
(preparation of insulin derivs.)
IT 69888-86-4 120177-51-7 184045-66-7 184045-67-8 184181-58-6
184493-04-7 184493-05-8 184493-06-9 184493-07-0 184493-08-1
184493-09-2 184493-10-5 184493-11-6 184493-12-7 184493-13-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of insulin derivs.)
IT 184181-46-2P 184181-48-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of insulin derivs.)

L29 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Albumin Binding and Time Action of Acylated Insulins in Various
Species
AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib;
Kiehr, Benedicte; Ribel, Ulla; Markussen, Jan
PY 1996
SO Journal of Pharmaceutical Sciences (1996), 85(3), 304-8

CODEN: JPMSAE; ISSN: 0022-3549

TI Albumin Binding and Time Action of Acylated Insulins in Various Species

AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib;

Kiehr, Benedicte; Ribel, Ulla; Markussen, Jan

AB Insulins acylated with fatty acids at the ϵ -amino group of NeB29 constitute a new class of insulin analogs, which are prolonged-acting due to albumin binding. In the present study it is shown that the affinity of fatty acid acylated insulins for albumin varies considerably (>50-fold) among species. The relative affinities of acylated insulin for albumin in human, pig, and rabbit serum are about 1:1.5:35. The severalfold higher binding affinity in rabbit serum than . . . pig serum and human serum, the pig model should provide a useful estimate of the degree of protraction of acylated insulin in humans. The results emphasize that species differences in ligand binding can be of major importance in the preclin. evaluation.

ST acylated insulin albumin binding

IT Rabbit

Swine

(albumin binding and time action of acylated insulins in various species)

IT Albumins, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(albumin binding and time action of acylated insulins in various species)

IT 11061-68-0D, Human insulin, NeB29-fatty acylated

derivs. 169148-58-7 169148-62-3 169148-63-4

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(albumin binding and time action of acylated insulins in various species)

L29 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

TI Albumin binding of insulins acylated with fatty acids:

characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo

AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib;

Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; Markussen, Jan

PY 1995

SO Biochemical Journal (1995), 312(3), 725-31

CODEN: BIJOAK; ISSN: 0264-6021

TI Albumin binding of insulins acylated with fatty acids:

characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo

AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib;

Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; Markussen, Jan

AB Albumin is a multifunctional transport protein that binds a wide variety of endogenous substances and drugs. Insulins with affinity for albumin were engineered by acylation of the ϵ -amino group of LysB29 with saturated fatty acids containing 10-16 carbon atoms. The association consts. for binding of the fatty acid acylated insulins to human albumin are in the order of 104-105 M-1. The binding apparently involves both non-polar and ionic interactions with the protein. The acylated insulins bind at the long-chain fatty acid binding sites, but the binding affinity is lower than that of the free fatty. . . . relatively small degree on the number of carbon atoms in the fatty acid chain. Differences in affinity of the acylated insulins for albumin are reflected in the relative timing of the blood-glucose-lowering effect after s.c. injection into rabbits. The acylated insulins provide a breakthrough in the search for soluble, prolonged-action insulin prepns. for basal delivery of the hormone to the diabetic patient. We conclude that the biochem. concept of albumin binding can be applied to protract the effect of insulin, and suggest that derivatization with albumin-binding ligands could be generally applicable to prolong the action profile of peptide drugs.

ST albumin binding acylated insulin prolonged action

IT Blood sugar
(albumin binding of insulins acylated with fatty acids
prolong blood sugar-lowering action)

IT Fatty acids, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(albumin binding of insulins acylated with fatty acids
prolong blood sugar-lowering action)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(albumin binding of insulins acylated with fatty acids
prolong blood sugar-lowering action)

IT 9004-10-8D, Insulin, acylated with fatty acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(albumin binding of insulins acylated with fatty acids
prolong blood sugar-lowering action)

L29 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

TI Insulin derivatives.

AU Markusson, Jan [Inventor, Reprint Author]; Jonassen, Ib [Inventor]; Havelund, Svend [Inventor]; Brandt, Jakob [Inventor]; Kurtzhals, Peter [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]

PY 2003

SO Official Gazette of the United States Patent and Trademark Office Patents, (Sep 16 2003) Vol. 1274, No. 3. <http://www.uspto.gov/web/menu/patdata.html>
e-file.
ISSN: 0098-1133 (ISSN print).

TI Insulin derivatives.

AU Markusson, Jan [Inventor, Reprint Author]; Jonassen, Ib [Inventor]; Havelund, Svend [Inventor]; Brandt, Jakob [Inventor]; Kurtzhals, Peter [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]

AB The present invention relates to insulin derivatives in which a lipophilic group having from 12 to 40 carbon atoms is attached to the alpha-amino group of the.

IT Major Concepts
Pharmacology

IT Chemicals & Biochemicals
insulin derivatives: antidiabetic-drug,
hormone-drug, metabolic-drug

RN 9004-10-8D (insulin derivatives)

L29 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

TI Insulin derivatives.

AU Markusson, Jan [Inventor, Reprint author]; Jonassen, Ib [Inventor]; Havelund, Svend [Inventor]; Brandt, Jakob [Inventor]; Kurtzhals, Peter [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]

PY 2001

SO Official Gazette of the United States Patent and Trademark Office Patents, (June 26, 2001) Vol. 1247, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.

TI Insulin derivatives.

AU Markusson, Jan [Inventor, Reprint author]; Jonassen, Ib [Inventor]; Havelund, Svend [Inventor]; Brandt, Jakob [Inventor]; Kurtzhals, Peter [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]

AB The present invention relates to insulin derivatives in which a lipophilic group having from 12 to 40 carbon atoms is attached to the alpha-amino group of the.

IT Major Concepts
Pharmacology

IT Chemicals & Biochemicals
insulin derivatives: hormone-drug

L19 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
TI Trials of lipid modification of peptide hormones for intestinal delivery
AU Muranishi, Shozo; Murakami, Masahiro; Hashidzume, Minoru; Yamada, Keigo;
Tajima, Shigeru; Kiso, Yoshiaki
PY 1992
SO Journal of Controlled Release (1992), 19(1-3), 179-88
CODEN: JCREEC; ISSN: 0168-3659
AB . . . study the intestinal delivery of peptide, three typical peptide hormones with different mol. wts., TSH-releasing hormone (TRH), tetragastrin (TG) and insulin, were used. With the aim of increasing peptide lipophilicity, these peptides were chemically modified by attaching fatty acid moieties (acyl chains) to their amino termini; this was achieved without marked loss of pharmacological activities. By reverse-phase HPLC, the synthesized peptide analogs, lauroyl-TRH, caproyl- and lauroyl-TG, and B1-monopalmitoyl- and B1, B29-dipalmitoyl-insulin, were confirmed to be more lipophilic than their parent peptides. These analogs retained more than 64% of the pharmacological activities of the parent peptides, as assessed following i.v. injection in rats. The results obtained showed that the lipophilic derivs. were more suitable for intestinal absorption than the parent peptides and that the stabilities of some derivs. against intestinal enzymatic degradation were improved. These findings suggest that, by appropriate lipid modification of the amino-terminus of peptides, it may be feasible to improve their intestinal delivery characteristics and their protective capabilities against enzymatic degradation

L14 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
TI Soluble, prolonged-acting insulin derivatives. II.
Degree of protraction and crystallizability of insulins substituted in positions A17, B8, B13, B27 and B30
AU Markussen, J.; Diers, I.; Engesgaard, A.; Hansen, M. T.; Hougaard, P.; Langkjaer, L.; Norris, K.; Ribel, U.; Soerensen, A. R.; et al.
PY 1987
SO Protein Engineering (1987), 1(3), 215-23
CODEN: PRENE9; ISSN: 0269-2139
TI Soluble, prolonged-acting insulin derivatives. II.
Degree of protraction and crystallizability of insulins substituted in positions A17, B8, B13, B27 and B30
AB . . . by B27 lysine or arginine substitutions and by B13 glutamine. The B27 residue is located on the surface of the hexamer, so a basic residue in this position presumably promotes the packing of hexamers at neutral pH. The B13 residues cluster in the center of the hexamer. When the electrostatic repulsive forces from 6 glutamic acid residues are abolished by substitution with glutamine, a stabilization of the hexamer can be envisaged. The biol. potency of insulins was measured in the free fat cell assay and in the mouse.
ST mutagenesis gene insulin deriv prep; insulin deriv structure activity; crystal structure insulin deriv
IT Chains, chemical
(helical conformation of, of insulin derivs.)
IT Blood sugar
(insulin derivs. effect on, mol. structure in relation to)
IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by adipocyte, insulin derivs. effect on, mol. structure in relation to)
IT Bond angle
Conformation and Conformers
Crystal structure
(of insulin derivs.)
IT Adipose tissue, metabolism
(adipocyte, lipid metabolism by, insulin derivs. effect on, mol. structure in relation to)
IT Molecular structure-property relationship
(crystallization, of insulin derivs.)
IT Molecular structure-property relationship
(hydrophobicity, of insulin derivs.)
IT Molecular structure-biological activity relationship
(hypoglycemic, of insulin derivs.)
IT Molecular structure-biological activity relationship
(lipogenic, of insulin derivs.)
IT 9004-10-8DP, Insulin, derivs. 110068-59-2P
110068-60-5P 110068-61-6P 110068-62-7P 110068-64-9P 110068-67-2P
110068-70-7P 110068-71-8P 110068-72-9P 110068-73-0P 111775-84-9P
111775-85-0P 111775-86-1P 111775-87-2P 111775-88-3P 111775-89-4P
111775-90-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and biol. activity of, mol. structure in relation to)

L14 ANSWER 2 OF 3 MEDLINE on STN
TI Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen.
AU Nielsen F S; Jorgensen L N; Ipsen M; Voldsgaard A I; Parving H H
PY 1995
SO Diabetologia, (1995 May) Vol. 38, No. 5, pp. 592-8.
Journal code: 0006777. ISSN: 0012-186X.
AB . . . compared to soluble human insulin. The human insulin analogue B10Asp (mono/dimeric) is absorbed twice as fast as soluble human insulin (

hexameric). A double blind, randomised crossover study with a 1-month run-in period and two 2-month treatment periods was performed in 21. . .

CT . . .
drug therapy

Double-Blind Method

Drug Administration Schedule

Hemoglobin A, Glycosylated: AN, analysis

Humans

Injections, Intravenous

Insulin: AD, administration & dosage

*Insulin: AA, analogs & derivatives

*Insulin: TU, therapeutic use

Lipoproteins, HDL Cholesterol: BL, blood

Lipoproteins, LDL Cholesterol: BL, blood

Recombinant Proteins: AD, administration & dosage

Recombinant Proteins: TU, therapeutic use

Time Factors

Triglycerides: BL, . . .

CN 0 (Blood Glucose); 0 (Hemoglobin A, Glycosylated); 0 (Lipoproteins, HDL Cholesterol); 0 (Lipoproteins, LDL Cholesterol); 0 (Recombinant Proteins); 0 (Triglycerides); 0 (insulin, Asp(B10)-)

L14 ANSWER 3 OF 3 MEDLINE on STN

TI Semisynthetic des-(B27-B30)-insulins with modified B26-tyrosine.

AU Lenz V; Gattner H G; Sievert D; Wollmer A; Engels M; Hocker H

PY 1991

SO Biological chemistry Hoppe-Seyler, (1991 Jul) Vol. 372, No. 7, pp. 495-504.

Journal code: 8503054. ISSN: 0177-3593.

AB . . . formal transpeptidation product at ArgB22--was formed in one step. Biological in vitro properties (binding to cultured human IM-9 lymphocytes, relative lipogenic potency in isolated rat adipocytes) of all semisynthetic analogues are reported, ranging from slightly decreased to two-fold receptor affinity and. . . typical of native insulin can be observed, and the CD-spectral effects in the near UV spectrum related to association and hexamerization of the native hormone are qualitatively reestablished. The results of this investigation underline the importance of position B26 to the. . .

CT Amino Acid Sequence
Circular Dichroism
Humans

*Insulin: AA, analogs & derivatives

Insulin: BI, biosynthesis

Molecular Sequence Data

Peptide Biosynthesis

*Peptide Fragments: BI, biosynthesis

Research Support, Non-U.S. Gov't

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	30801	insulin and derivativ?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L2	3754	hexamer?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L3	0	hexamer*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L4	29	hexamer???	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L5	968	hexamer??	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L6	840	I1 and I2	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L7	108	I6 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L8	49	I6 and @py<"1998"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L9	0	I8 and stab?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L10	19	I8 and life	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L11	43	I8 and composition	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L12	29	I11 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L13	0	I7 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L14	19	I7 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L15	19	I14 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:40

EAST Search History

L16	17	I15 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L17	25	markussen adj jan	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L18	32	havelund near svend	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L19	8	brandt near jakob	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L20	7	kurtzhals near peter	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L21	50	I17 or I18 or I19 or I20	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L22	50	I21 and insulin	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L23	36	I22 and derivative?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L24	13	I23 and hexameric	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L25	0	I24 and lipo	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L26	0	I24 and lipo*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L27	0	I24 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L28	13	I24 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:47